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Comment on the April 26, 2007 Report of the NIEHS Review Panel on the Centers for Children's Environmental Health and Disease Prevention Research Program

Dear Dr. Schwartz:

We write to express our grave concern that the recommendations put forth by the Review Panel on the Centers for Children's Environmental Health and Disease Prevention Research have the potential, if implemented by NIEHS, to do irreparable damage to the Children's Environmental Health Centers Program and to slow the extraordinary progress that has been made over the past decade in increasing understanding of the preventable environmental causes of the most important diseases confronting American children today – asthma, autism, attention deficit/hyperactivity disorder (ADHD), birth defects, reproductive impairment, and neurobehavioral dysfunction.

The Children's Environmental Health Centers Program has been highly productive and has contributed greatly to our enhanced understanding of the environmental causes of childhood disease. The Program has successfully translated state-of-the-art information on developmental toxicology and environmental genomics to exploration of the causes and mechanisms of disease in children living in communities across the United States. The Program has catalyzed development of the new subspecialty of environmental pediatrics. The Program has the clear potential to generate enormously important information on the environmental causes of disease among children in developing countries, nations in which the environmental exposures are often more intense, and the susceptibility possibly even greater than among children in the United States. The Program has begun successfully to guide evidence-based prevention of disease.

Overview. Review of the Children's Environmental Health Centers Program is certainly appropriate after nearly a decade of funding. Strong, visionary and constructive review has the potential to strengthen the Program and to accelerate incorporation into the Centers' research portfolio of new developments in basic science. But such review needs to be carefully balanced and fully cognizant of the fact that the multi-year, prospective epidemiologic studies of birth cohort that are the heart of the Centers Program take many years to develop and to yield research results. These well

characterized, closely studied populations are the proving ground for testing advances in basic science, they are difficult and very costly to develop, and they should be regarded as an invaluable national treasure. We are concerned that many of the accomplishments of the Centers, and in particular the scientific advances that have been and will continue to be generated by the birth cohorts, appear to have been ignored or at least given short shrift by the Review Panel.

A key recommendation of the Review Panel is that the primary research focus of the Children's Centers should move away from the current emphasis on epidemiologic studies of the diseases affecting children in communities to basic science. In the view of the Panel (section 2.2), the Centers need:

"To move beyond exclusive primary prevention toward inclusion of additional prevention strategies as well as the development of therapeutics."

Despite reassuring words to the contrary, it is clear that the Panel perceives the funding of the Centers to be an "either/or" proposition in which a stark choice must be made between either supporting epidemiologic studies of children in communities or supporting basic science. Short-sightedly, in our opinion, the Panel members have recommended radical revisions in the Children's Centers program and in its fiscal architecture that will divert the program away from investigation of the major diseases of environmental origin affecting children in the United States and turn it into a laboratory-based program of developmental toxicology and drug discovery. Our fundamental concern is that the Panel's recommendations –especially those that call for sharply reducing community engagement - will lead to unraveling of the children's cohorts just as these cohorts are beginning to mature. Opportunities within the cohorts to examine the impacts of early environmental exposures on cognitive development, on the genesis of autism and ADHD, on school performance, on disruptions of pubertal development, and on mental health problems such as depression and schizophrenia, will all be lost.

The danger inherent in a radical revision of the Centers Program such as that recommended by the Review Panel is that it misses opportunities to bridge disciplines and to incorporate promising new developments in developmental biology, genomics and epigenetics into the existing birth cohort studies. Rather than seek innovative opportunities to translate the latest developments in laboratory science into the community and to field-test them in these well characterized cohorts for the ultimate betterment of children's health, the Panel proposes instead a retreat to the laboratory. Implementation of this narrow-minded approach will waste a decade of investment and miss substantial opportunities to advance science and to prevent disease.

Composition of the Review Panel. A fundamental problem is that the Review Panel was highly skewed in its composition. Despite its avowed focus on children's health, the Panel did not contain a single pediatrician. It included only one very devoted, but very junior person from the children's environmental health advocacy community. Yet at the same time, the Panel contained an abundance of very senior, highly accomplished laboratory scientists who have studied genomics,

epigenetics and the developmental impacts of environmental toxins in experimental settings. Given this make-up, it is perhaps not surprising that the Panel chose to devalue child-centered epidemiologic studies and to devalue primary prevention of environmental diseases – the proven most effective approach to prevention - while urging increased investment in laboratory-based research and encouraging drug discovery.

The Birth Cohort Studies – A National Treasure. The birth cohort studies are the centerpiece of the Children’s Centers program. These cohorts have followed approximately 1,500 children from early in pregnancy, through infancy and into childhood; the children in the earliest established cohorts are now 6-7 years old. These studies have characterized the health status of each of the children in them in remarkable detail. To discover new information about environmental risk factors, susceptibility, and disease mechanisms for the most important diseases confronting American children, the cohort studies have assessed maternal and childhood exposures to environmental toxicants during pregnancy and after birth in real time as the exposures actually occurred using state-of-the-art environmental monitoring and newly developed biomarkers, precisely the approach that David Schwartz and Francis Collins advocate in their scholarly commentary in this week’s *Science* magazine. They have banked thousands of biological and environmental samples.

The banked samples from the cohort studies can be utilized to support precisely the types of genomic and epigenetic investigations that the Review Panel advocates. Investigators from across the Centers have pooled data nationally from their cohorts to examine the consequences on children’s cognitive development of early exposures to organophosphate pesticides and PCBs. These analyses have shown that early exposures can cause developmental delays, loss of IQ, increased risk of ADHD and increased risk of Pervasive Developmental Disorder [a condition akin to autism]. These data have provided an evidentiary basis for primary prevention and have guided specific public health actions such as limiting the residential use of the OP pesticides, chlorpyrifos and diazinon. The scientific findings of the Centers have thus already protected tens of thousands of American children from prenatal brain injury. The Panel acknowledges these successes in Section 3.1.

Among the scientific accomplishments to date of the Children’s Centers birth cohorts studies are the following:

- The Mount Sinai Center for Children's Environmental Health and Disease Prevention Research has conducted a prospective birth cohort study that has documented that babies exposed *in utero* to the organophosphate insecticide chlorpyrifos had smaller head circumference at birth than unexposed peers and that these children had delays in cognitive development. This study found additionally that the effect of chlorpyrifos on head circumference was evident only in children born to mothers with low expression levels of the pesticide-metabolizing enzyme paraoxonase (PON1). This represents a newly discovered gene-environment interaction.
- The Mount Sinai Children’s Center has recently expanded the scope of research in its birth cohort study and is now examining the impacts on child development of early exposures to endocrine disruptors, particularly phthalates and bisphenol A. This expansion of the research was possible at modest cost because the cohort was already established and several

thousand biological samples had already been banked and were available for analysis. Of especial concern is the possibility that early life exposures to endocrine disruptors may accelerate the onset of puberty and thus increase future risk of breast cancer and heart disease in American women.

- The Mount Sinai Children's Center conducted a community-based intervention project in East Harlem, demonstrating that it is indeed feasible and highly cost-effective to reduce pesticide use and to introduce integrated pest management (IPM) to an inner-city community. These results have been accepted city-wide by the New York City Housing Authority and will result therefore in reductions in pesticide exposure for tens of thousands of children.
- The Mount Sinai Children's Center conducted a prospective epidemiological study of babies born to mothers acutely exposed to dust and smoke from the World Trade Center. This study found a doubling in incidence of small for gestational age (SGA) babies born to exposed mothers compared to unexposed, socioeconomically similar controls.
- The Columbia Center for Children's Environmental Health (CCCEH) is conducting a prospective cohort study in a culturally diverse urban population residing in Washington Heights, Central Harlem, and the South Bronx, New York City. Data on Environmental Tobacco Smoke (ETS) from this study show widespread, prenatal exposures to polycyclic aromatic hydrocarbons (PAH) and ETS; significant downward shifts in the distribution of birth weight, birth length, and/or head circumference among children prenatally exposed to elevated levels of these contaminants; significant downward shifts in the distribution of 2-year cognitive development scores among children prenatally exposed to ETS; and evidence that the developmental effects of prenatal ETS exposure are more severe for children born into families with high exposure to social adversity:
- Data on pesticide exposure from the Columbia Children's Center cohort show significant adverse effects of prenatal organophosphate pesticide exposure on cognitive and motor development in 3-year-old infants. These studies found that prenatal exposures to organophosphates are associated with increased rates of behavior problems, specifically ADHD and Pervasive Developmental Disorder.
- Data from the prospective birth cohort study in the Cincinnati Children's Center documented that extremely low levels of exposure to lead – levels that are widespread among American children today and that were previously considered safe – have adverse effects on neurocognitive development in infants and are associated with diminished intelligence and learning disabilities in children. The Cincinnati studies have identified genes that increase the sensitivity of certain children to lead. These findings have major implications nationally for lead poisoning prevention programs.
- Data from the cohort study in the California Children's Center at UC Berkeley have documented that prenatal exposures to organophosphate pesticides are associated with slowed mental development and persistent developmental problems in 2-year-old children.

- Data from the University of Iowa Children's Center have shown that asthma is nearly as highly prevalent among rural children as it is among children in inner cities, a break-through finding. The Iowa studies have generated important information on preventable environmental triggers for asthma, most notably endotoxins, among farm children.
- Data from the Children's Center at Johns Hopkins have documented strong linkages between urban air pollution and childhood asthma. These studies have explored the mechanisms by which particulate pollution causes asthma and have sought to discover genes that increase individual susceptibility to asthma in certain children.
- The Center at the University of Southern California has generated what are possibly the best data in the world on the relationship between fine airborne particulate pollution and childhood asthma. In an enormous analysis that spanned the entire Los Angeles basin, researchers from this Center found sharply higher rates of asthma and significantly diminished rates of lung growth among children residing in the most heavily polluted communities. These studies have also shown links between early life exposure to particulate pollutants and coronary heart disease, the major killer of American adults.

Proposed Changes in Funding Mechanism. The Review Panel recommends a radical change in the funding mechanism for the Children's Centers. They propose to change these Centers from operating centers that directly support multidisciplinary research such as the birth cohort studies into centers that support only research infrastructure. The Panel recommends that future research in the Children's Centers be sustained via the RO1 grant mechanism, and they suggest that to qualify as a Children's Center an institution must possess three RO1 grants in relevant areas of research and that these initial three grants be followed by two more.

We consider this new funding mechanism to be problematic. It threatens the stability of the Children's Centers, impedes the interdisciplinary interactions that have characterized research within and across the Centers, threatens to disrupt the continuity of the Centers' prospective birth cohort studies, and impedes efforts to translate recent developments in laboratory science into community and clinical settings. This proposed new mechanism is one that will substantially favor laboratory research at the expense of clinical translation and primary prevention.

Conclusion. We are deeply concerned that if the narrowly conceived recommendations of the Review Panel for the Children's Environmental Health Centers Program are adopted by NIEHS, they will irreparably damage the research program in Children's Health and the Environment that NIEHS and EPA have so carefully nurtured over the past decade. Translation of basic science to clinical application and primary prevention will go backward, reversing the remarkable accomplishments in the Children's Centers. The birth cohort studies that the Children's Centers have so painstakingly constructed and diligently pursued - studies that have become a national treasure - will likely be destroyed.

We urge you and the NIEHS Council to give the recommendations of the Review Panel very close scrutiny and to examine them with more than a little skepticism. We suggest that you contrast and compare the starkly worded recommendations of the NIEHS Review Panel with the much more measured recommendations on the future of the Children's Environmental Health Centers Program that have been offered by your counterparts in the Office of Research and Development of the US Environmental Protection Agency.

We suggest further that, difficult as it may be, you consider convening a new Review Panel that embodies a wider range of points of view than are represented in the current Panel and that specifically includes senior scientists from the fields of pediatrics, public health and preventive medicine. Their voices will complement and enrich those of the basic scientists. We suggest that such a new Panel may offer NIEHS a much more carefully considered strategy that, instead of advocating retreat to the laboratory, will suggest innovative new approaches for translating developmental biology to epidemiology, disease prevention and clinical medicine thus substantially strengthening the Centers for Children's Environmental Health and Disease Prevention Research Program and protecting the health of America's children.

Sincerely,

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